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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of Biotechnology Activities; Recombinant DNA Research: Proposed Actions under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

SUMMARY: The NIH Office of Biotechnology Activities (NIH OBA) proposes to revise the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) to streamline review of certain human gene transfer trials that present a low biosafety risk. Specifically, the NIH OBA proposes to remove the requirement that institutional biosafety committees (IBCs) review and approve certain human gene transfer clinical trials that use plasmids and certain attenuated, non-integrating viral vectors, provided the clinical trial follows an initial study in humans that was previously approved by an IBC registered with the OBA. This initial trial will have established the safety of the proposed dose of the gene transfer product (vector and transgene) in a comparable population (adults or children). The initial study should have been conducted in the same country as the proposed study to control for potential variability in infectious disease backgrounds of the participants.

An initial IBC review is important to evaluate the safety of the product and to set standards for administration; however, for well-characterized vectors, in the absence of

any unexpected toxicities in the initial study, subsequent biosafety assessments may not provide any additional information. While a single IBC review does not pose an undue burden, as the gene transfer field advances and more Phase II and Phase III multisite trials are developed, the time, effort and expense associated with multiple IBC reviews can be significant without adding commensurate value in the form of additional recommendations to protect the health and safety of the subject, health care worker, and community.

IBCs play a critical role in the evaluation of new products and their review can inform other oversight bodies, such as Institutional Review Boards. However, given the competing demands on IBCs, this change will provide IBCs with the option of focusing their efforts on those clinical trials where review will be most productive. While IBCs will no longer be required to review all clinical trials using the same product, each institution can implement its own policies regarding the need to review such trials and the information that a principal investigator (PI) should submit regarding the safety of the previous trial. For example, an institution may designate the Biological Safety Officer and the IBC Chair to review data from the initial trial and determine whether a subsequent trial using the same agent meets the exemption criteria outlined herein. The institution may also set its own policies regarding the need for the PI to inform the IBC about enrollment, any relevant new biosafety findings, and completion of the trial.

This policy will only exempt human gene transfer clinical trials from IBC review under Section III-C-1. It does not apply to basic, nonclinical research. In addition, it does not create an exemption from registration of the trial with the NIH OBA or the Recombinant DNA Advisory Committee (RAC) review and reporting requirements. By

continuing to require registration and reporting on these trials, the NIH OBA will be able to continue to monitor adverse events or incident reports of accidental exposures by health care workers delivering these agents and, if necessary, provide information regarding these events to investigators, IBCs, and the public. The NIH OBA will also be able to assess whether this change in policy has any adverse impact on the biosafety of gene transfer trials.

DATES: All comments should be submitted by [insert date 30 days after publication].

ADDRESSES: Comments may be submitted to the NIH OBA by e-mail at oba@od.nih.gov; by fax to 301-496-9839; or by mail to the NIH Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892-7985. All written comments received in response to this notice will be available for public inspection in the NIH Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland, weekdays between the hours of 8:30 a.m. and 5:00 p.m.

FOR FURTHER INFORMATION: If you have questions, or require additional information about these proposed changes, please contact the NIH OBA by e-mail at oba@od.nih.gov or telephone at 301-496-9838. Comments can be submitted to the same e-mail address or by fax to 301-496-9839 or mail to the NIH Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, MD

20892-7985. Background information may be obtained by contacting the NIH OBA by e-mail at oba@od.nih.gov.

SUPPLEMENTARY INFORMATION: Human gene transfer is a maturing field. There are currently over 1,200 gene transfer trials registered since 1988 with the OBA. While the majority of trials are still small safety studies, increasingly Phase II and III multisite trials are being initiated. IBCs play a critical role in the evaluation of human gene transfer trials. IBCs identify and manage biosafety issues raised by gene transfer agents, including safety issues that may arise due to the nature of the vector. The IBC assesses the risks of horizontal and vertical viral vector transmission and provides guidance on the safe handling and administration of the product in a context that considers the local clinical environment. The IBC also examines the preclinical data that support the safety of the vector as delivered. Finally, the IBC reviews the informed consent to ensure that the risks that arise from the biological nature of the vector are clearly stated.

Investigators have noted that repeated reviews by multiple IBCs of a multisite Phase II or III trial have often not resulted in new recommendations and such reviews can impose a cost on the research, including the cost of establishing IBCs at sites without pre-existing IBCs and the time required to complete multiple reviews. The NIH OBA recognizes that the biosafety profiles of many vectors are well characterized, and while the transgene may have an impact on the safety profile, an IBC may be able to identify most of the issues through the review of the initial trial. In addition, members of the RAC, some of whom have served on IBCs, also note that providing IBCs some discretion in whether to review certain low risk clinical trials is desirable.

In order to identify the type(s) of trials that might qualify for an exemption from further IBC review, the NIH OBA considered the types of vectors that have been frequently used in gene transfer protocols over a number of years. The NIH OBA concluded, with the advice of the RAC, that gene transfer products that employ plasmids or attenuated Risk Group (RG) 2 viruses that are not designed to integrate into the host genome are of sufficiently low biosafety risk to be considered for this exemption. The vectors OBA proposes to make eligible for this exemption are derived from the following viruses: adenoviruses, serotypes 2 and 5; herpes simplex viruses 1 (HSV-1); adeno-associated viruses (AAV); and poxviruses, except for vaccinia. While AAV vectors do integrate, given the safety record to date with AAV vectors and the fact that they are more likely to remain episomal, including them in this exemption is appropriate. Research with vaccinia vectors was not considered eligible for the exemption because of the adverse events that were documented when vaccinia was used as a vaccine against smallpox and reports of skin pustules developing in some research participants receiving intravenous administration of vaccinia vectors in gene transfer protocols. Continued oversight by an IBC to ensure proper handling and administration of vaccinia vectors seems prudent. Clinical research with integrating vectors, including transposons, is not eligible for this exemption due to the need for long-term follow-up; therefore IBC oversight is again appropriate.

A list of viruses eligible for this exemption will be presented in a new section of Appendix B (Appendix B-V-2) that will be titled Viruses used as Vectors for Human Gene Transfer that Present Low Biosafety Risk and are Eligible for Exemption from IBC Review under Section III-C-1. This list can be updated by the NIH OBA, in consultation

with the RAC chair and one or more RAC members as needed. (See Minor Actions in the NIH Guidelines Section IV-C-1-b-(2).) As experience grows with other vectors, they may also become eligible for this exemption and will be added to Appendix B-V-2.

Almost all viral vectors used in gene transfer are attenuated compared to the wild-type virus. To be exempt from IBC review, there must be data that the vector is attenuated compared to the wild type virus; this data should be provided from both animal models and the previous clinical trial. Attenuation may be achieved by gene deletions or irreversible mutations in genes required for cell-to-cell transmission or virulence.

In order to be exempt from IBC review, in addition to using one of the specified vectors, an initial clinical trial must have been conducted using the same gene transfer product. This initial trial may not be a single subject protocol or what is sometimes referred to as a “compassionate use trial.” An initial safety trial, or Phase I trial, may be used to support the exemption of a Phase II trial while an initial safety trial, Phase I, or a Phase II trial may be used to support the exemption of a Phase III trial. The design of the proposed trial should be comparable to the previous clinical study that is being used to justify an exemption from IBC review. This ensures that the safety data from the initial trial is applicable to the subsequent trials. Specifically, the dose(s) of the gene transfer agent to be used in the Phase II or III trial must be equal to or less than the dose administered in the safety trial and the delivery route must be identical, e.g., a trial using intramuscular delivery would not support exemption of a trial using intravenous administration, as the biodistribution of the product may be quite different. Chemotherapy, radiation, and other immune modulatory agents can also potentially alter

the biodistribution and/or shedding of the vectors due to effects on the immune system. Consequently, if concomitant chemotherapy or radiotherapy will be administered with the gene transfer agent, the co-administration of these agents must have been tested in the initial safety trial.

Also the population enrolled in the initial trial must be comparable to the population in the proposed trial. The NIH OBA recognizes that there are many clinical factors that affect the safety of a product in a certain population, including co-morbidities and type of disease. However, in order to have an exemption that can be uniformly applied across IBCs, the proposed exemption focuses on two factors: the age of the subject and the infectious disease background. In drug development, it is recognized that children are not simply small adults. Children's immune systems are different and the pharmacokinetics of viral vectors in pediatric patients may be altered; therefore, an initial safety study must be conducted in a pediatric population before exempting subsequent studies in pediatric populations.

Another issue is whether the safety profile of a product will differ if the population has significantly different background exposure to infectious diseases, as many of the vectors proposed to be included in this exemption are viral vectors. Even within the U.S. there can be differences in the prevalence of certain infectious diseases; however, it is likely that those differences may be more pronounced between different countries, as certain infectious diseases are endemic in some countries but rarely observed in others. That is not to say that the infectious disease background is always significantly different across countries (for example one would not expect significant differences between the U.S. and Canada), but in order to make this criterion easily

interpretable by the IBC, the clinical protocol that will be the basis for exempting review of subsequent protocol(s) must have been conducted in the same country. This will also ensure that an IBC in the country in which the trial will be conducted has carried out a review of the product.

The main impetus for this proposed policy change is to facilitate multisite trials that follow an initial Phase I safety trial or a Phase II study by removing the requirement for multiple IBC reviews for a well-characterized agent. When a trial is only conducted at a single site, the burden of a single IBC review should not be significant or unduly delay the research. Therefore, the original intent was to limit this exemption to trials that would be conducted at more than one site, including at sites that might not already have an IBC. However, it is possible that one might conduct an initial safety study at a single site and conduct the next study with an identical design at a single site, perhaps because the available population in which to study the disease is limited. Given that there is no scientific rationale for limiting the IBC review exemption only to subsequent multisite trials, and since an IBC can still choose to review the trial, the NIH OBA concludes that the exemption should apply to all studies that meet the above criteria, be they single or multisite trials.

The NIH OBA has used the terms Phase II and Phase III in this notice to describe the type of trial that would be exempt under this new policy. These terms are used because they are typically the way studies are classified as they progress through the FDA regulatory process. However, the NIH OBA recognizes that such labels are not all inclusive and there may be Phase I/II trials that follow an initial safety study. Therefore, rather than limiting the exemption to just Phase II or Phase III trials, the policy focuses

instead on having data from at least one comparable trial. The NIH OBA also recognizes that the initial study may be a small safety study of ten to 20 subjects, which is not unusual in gene transfer trials, and that such trials do not definitively establish the safety of the product. Indeed, safety data continue to emerge throughout the life cycle of a drug or biologic agent, including after licensing. Nonetheless, given the experience with the vectors eligible for an exemption, it is anticipated that the types of safety issues of most concern to an IBC will likely emerge during the review of the documentation submitted in support of the initial clinical trial and the clinical experience from the initial trial. Again, IBCs have the institutional prerogative to require registration of trials and can decide to review certain trials if new data emerges.

The determination of whether a trial meets this exemption from IBC review should be made by the local IBCs. The initial trial, whether done at one or more sites, requires IBC review. For the subsequent trials using the same agent, if they will be conducted only at sites that receive NIH funding for recombinant or synthetic nucleic acid research, then these sites should already have an IBC registered with the NIH OBA. If the sponsor or a site investigator concludes that their trial meets the exemption criteria, this should be confirmed by at least one IBC at one of the trial sites. Institutions with IBCs should establish a policy for how to handle protocols that are eligible for exemption. An IBC may require that the PI at that site or the sponsor register and provide an abbreviated summary of the data from the first trial to confirm that the trial indeed meets the exemption criteria. An institution may also decide to rely on a decision by another IBC that the protocol is eligible to be exempt. The NIH OBA has proposed

exemption criteria that are objective to facilitate uniform decisions across IBCs.

However, the NIH OBA is available to provide guidance and clarification upon request.

In some cases, a non-NIH-funded trial will be conducted both at sites that receive NIH funding for recombinant or synthetic nucleic acid research—and therefore have IBCs—and at non-NIH-funded sites that do not have IBCs. In this situation, the NIH OBA expects the individual responsible for the conduct of the trial to confirm with an established IBC at one of the institutions that their trial does not require IBC review before initiating the trial at a site that does not have an IBC. It is also possible that the trial could be funded by NIH, or by an NIH-funded Institution, but the trial will be conducted only at non-NIH-funded sites that do not have IBCs, for example clinics or community hospitals that do not receive NIH funding for recombinant or synthetic nucleic acid research. In this situation, because it is subject to the NIH Guidelines, the trial must be reviewed by an IBC at each trial site, even if the site does not receive funding from NIH for recombinant or synthetic nucleic acid research. However, there would not necessarily be IBCs established at the planned trial sites to make a determination regarding whether the trial meets the exemption criteria. It would not make sense to set up an IBC solely to determine if a trial is exempt from IBC review. The PI or sponsor should consult with the NIH OBA regarding whether the trial is exempt from review.

To implement this exemption, the following proposed changes will be made to Section III-C and to Appendices M-I-C-1, M-I-C-2, and B. The current Section III-C-1 states:

Section III-C-1. Experiments Involving the Deliberate Transfer of Recombinant or Synthetic Nucleic Acid Molecules, or DNA or RNA Derived from Recombinant or Synthetic Nucleic Acid Molecules, into One or More Human Research Participants

Human gene transfer is the deliberate transfer into human research participants of either:

1. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or
2. Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules, that meet any one of the following criteria:
 - a. Contain more than 100 nucleotides; or
 - b. Possess biological properties that enable integration into the genome (e.g., cis elements involved in integration); or
 - c. Have the potential to replicate in a cell; or
 - d. Can be translated or transcribed.

No research participant shall be enrolled (see definition of enrollment in [Section I-E-7](#)) until the RAC review process has been completed (see [Appendix M-I-B, RAC Review Requirements](#)).

In its evaluation of human gene transfer proposals, the RAC will consider whether a proposed human gene transfer experiment presents characteristics that warrant public RAC review and discussion (See [Appendix M-I-B-2](#)). The process of public RAC review and discussion is intended to foster the safe and ethical conduct of human gene transfer experiments. Public review and discussion of a human gene transfer experiment (and access to relevant information) also serves to inform the public about the technical aspects of the proposal, meaning and significance of the research, and any significant safety, social, and ethical implications of the research.

Public RAC review and discussion of a human gene transfer experiment may be: (1) initiated by the NIH Director; or (2) initiated by the NIH OBA Director following a recommendation to NIH OBA by: (a) three or more RAC members; or (b) a Federal agency other than NIH. After a human gene transfer experiment is reviewed by the RAC at a regularly scheduled meeting, NIH OBA will send a letter, unless NIH OBA determines that there are exceptional circumstances, within 10 working days to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate, summarizing the RAC recommendations.

For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in [Section I-E-7](#)) at the clinical trial site until the following documentation has been submitted to NIH OBA: (1) Institutional Biosafety Committee approval (from the clinical trial site);

(2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; (4) curriculum vitae of the Principal Investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

The fifth paragraph of Section III-C-1 will be amended to add “if required” at the end of the statement regarding IBC approval in order to recognize that some trials will not need IBC review. In addition, a new final paragraph outlining the exemption will be added. The new proposed language is as follows:

For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in [Section I-E-7](#)) at the clinical trial site until the following documentation has been submitted to the NIH OBA: (1) Institutional Biosafety Committee approval (from the clinical trial site), if required; (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; (4) curriculum vitae of the Principal Investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

Institutional Biosafety Committee review and approval will not be required for gene transfer protocols that meet all of the following criteria:

- 1) A previous clinical trial using this investigational gene transfer agent (vector and transgene) enrolled more than one subject and was reviewed by an Institutional IBC and is now complete.
- 2) The investigational gene transfer agent uses a plasmid or viral vector derived from a virus listed in Appendix B-V-2 that is: a) not designed to integrate, and b) attenuated compared to the wild-type virus or is not known to have ever caused disease in humans.
- 3) The previous clinical trial:
 - a. Was conducted in the same country as the proposed trial;
 - b. Enrolled a comparable population in terms of age (i.e. adult and/or pediatric); and
 - c. Tested a dose equal to or less than the dose proposed for the new trial, using the same administration route and, if concomitant interventions (e.g. radiation and/or chemotherapy) are proposed, they have been used in a prior trial with the same agent.

Appendix M-I-C-1 currently states:

Appendix M-I-C-1: Initiation of the Clinical Investigation

No later than 20 working days after enrollment (see definition of enrollment in Section I-E-7) of the first research participant in a human gene transfer experiment, the Principal Investigator(s) shall submit the following documentation to NIH OBA: (1) a copy of the informed consent document approved by the Institutional Review Board (IRB); (2) a copy of the protocol approved by the Institutional Biosafety Committee (IBC) and IRB; (3) a copy of the final IBC approval from the clinical trial site; (4) a copy of the final IRB approval; (5) a brief written report that includes the following information: (a) how the investigator(s) responded to each of the RAC's recommendations on the protocol (if applicable); and (b) any modifications to the protocol as required by FDA; (6) applicable NIH grant number(s); (7) the FDA Investigational New Drug Application (IND) number; and (8) the date of the initiation of the trial. The purpose of requesting the FDA IND number is for facilitating interagency collaboration in the Federal oversight of human gene transfer research.

Appendix M I-C-1 would be amended to again recognize that IBC approval may not be needed for every trial. The proposed Appendix M-I-C-1 is as follows:

Appendix M-I-C-1: Initiation of the Clinical Investigation

No later than 20 working days after enrollment (see definition of enrollment in Section I-E-7) of the first research participant in a human gene transfer experiment, the Principal Investigator(s) shall submit the following documentation to the NIH OBA: (1) a copy of the informed consent document approved by the Institutional Review Board (IRB); (2) a copy of the protocol approved by the Institutional Biosafety Committee (IBC) and/or IRB; (3) a copy of the final IBC approval from the clinical trial site, if required; (4) a copy of the final IRB approval; (5) a brief written report that includes the following information: (a) how the investigator(s) responded to each of the RAC's recommendations on the protocol (if applicable), and (b) any modifications to the protocol as required by FDA; (6) applicable NIH grant number(s); (7) the FDA Investigational New Drug Application (IND) number; and (8) the date of the initiation of the trial. The purpose of requesting the FDA IND number is for facilitating interagency collaboration in the federal oversight of human gene transfer research.

Appendix M-I-C-2 will likewise be revised to recognize that not all clinical trials will require IBC review. Appendix M-I-C-2 now states:

**Appendix M-I-C-2
Additional Clinical Trial Sites**

No research participant shall be enrolled (see definition of enrollment in Section I-E-7) at a clinical trial site until the following documentation has been submitted to NIH OBA: (1) Institutional Biosafety Committee approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; (4) curriculum vitae of the Principal Investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

The proposed Appendix M-I-C-2 is:

Appendix M-I-C-2

Additional Clinical Trial Sites

No research participant shall be enrolled (see definition of enrollment in Section I-E-7) at a clinical trial site until the following documentation has been submitted to the NIH OBA: (1) Institutional Biosafety Committee approval (from the clinical trial site), if required; (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; (4) curriculum vitae of the Principal Investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

A new section will be added to Appendix B.

Appendix B-V-2. Viruses used in Vectors for Human Gene Transfer that Present Low Biosafety Risk and are Eligible for Exemption from IBC Review under Section III-C-1

- Adenovirus, serotypes 2 and 5
- AAV, all serotypes
- Herpes Simplex virus 1
- Pox Viruses, with the exception of vaccinia

Dated: May 6, 2013

Lawrence A. Tabak,

Deputy Director

National Institutes of Health

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